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Non-Alcoholic Fatty Liver Disease (NAFLD), Adipocytokines and Diabetes Mellitus

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1. Introduction

Nonalcoholic fatty liver disease (NAFLD), which includes nonalcoholic steatosis and nonalcoholic steato- hepatitis (NASH), describes the clinicopathologic spectrum of alcohol-like liver disease in the nonalcoholic [Ludwig et al 1980].

Although it may be observed as an iatrogenic complication (due to drugs or anti-obesity surgery) or secondary to various other conditions (toxins, lipodystrophic syndromes, hypobetalipoproteinemia), NAFLD most commonly occurs as a primary (idiopathic) disease.

The clinical importance of primary NAFLD appears to rest on three main observations:

- It commonly occurs in the general population worldwide and among patients presenting with unexplained mild to moderate raised aminotransferase levels .
- It is not a sign or symptom of disease but it is a pathological condition that has the potential to progress to advanced hepatic and extrahepatic disease ,and to interact with other etiologies of liver disease .
- It may recur following orthotopic liver transplantation and poses a heavy burden of complications in the setting of major extrahepatic and liver-related surgery .

2. Reported risk factors

The conventional risk factors for the development of primary NAFLD include type II diabetes, insulin resistance, hyperlipidemia and obesity (Mezey,1998). NAFLD typically affects 50% of diabetics and 76% of obese patients (Bellantini et al 2000;Gupte et al.2004), and is the most common of all liver diseases. However, the prevalence of NASH is substantially less, affecting 18.5% of obese patients.

Other traditional risk factors include hyperuricemia, central obesity defined as waist circumference greater than 100 cm in males and greater than 88 cm in females, and hypertension.

Secondary causes of NAFLD include nutrition-related complications, such as total parenteral nutrition, rapid weight loss, and intestinal jejunoileal bypass surgery. Common causes of Steatosis is mention in Table.1.

Nonalcoholic fatty liver disease
Alcohol
Drugs—estrogens, coumadin, tamoxifen, valproic acid, methotrexate, isoniazid, corticosteroids, vitamin A, troglitazone, l-asparaginase, amiodarone, perhexiline, calcium channel blockers, nucleoside analogues
Hepatitis C (genotype 3)
Nutritional factors—rapid weight loss, total parenteral nutrition
Surgical considerations—gastrointestinal surgery for obesity, extensive small-bowel resection
Metabolic disorders—cystic fibrosis, abetalipoproteinemia, others
Syndromes associated with obesity, insulin resistance—lipodystrophies, hypopituitarism, Prader-Willi syndrome

Table 1. Conditions Associated With Macrovesicular Steatosis

Certain drugs are associated with NAFLD. Metabolic syndromes and pregnancy-related fatty liver diseases are also some of the secondary causes of NAFLD. Patients with normal body mass index (BMI) may develop NAFLD even in the absence of traditional risk factors. It is thought that the primary abnormality may be occult insulin resistance or central adiposity (Lee et al.1998).

The natural history of NAFLD still remains poorly defined. Mortality among NAFLD patients approaches 13%, which is greater than age- and sex-matched controls (6). Because these patients often have features of the metabolic syndrome, they are at high risk for cardiac-related death. Hence, both ischemic heart disease and malignancy are the leading causes of death in patients with NAFLD. However, liver disease is the third most common cause of mortality in this population, accounting for 13% of all deaths. This is significantly different than patients without NAFLD, in whom liver-related causes of mortality account for less than 1% of all deaths (Adams et al 2005). Clinical predictors of more advanced disease include people with diabetes, hypertriglyceridemia (Caldwell et al.1999) and those older than 40 years of age. Table.2. outlines the diagnostic criteria for NAFLD.

Parameter	Value
Impaired glucose tolerance	Fasting blood glucose l vel ≥110 mg/dL(5.6mmol/L)
High blood pressure	≥130/85 mm Hg
Elevated triglyceride levels	>250 mg/dL(1.7mmol/L)
Low high-density lipoprotein level	<40 mg/dL (1.00mmol/L)for men; <50 mg/dL(1.3mmol/L) for women
Abdominal obe ity	Waist: >102 cm (40 inches for men; >88 cm (35 inches) for women

Table 2. Diagnostic Criteria for the Metabolic Syndrome: Presence of Two or More of the Following Parameters

3. Diagnosis

Most patients with NAFLD are asymptomatic or suffer from nonspecific symptoms and signs such as fatigue, malaise or right upper quadrant pain. In most cases, the diagnosis is suspected in the context of the appropriate risk factor profile and incidental elevation of transaminases. Levels of aspartate aminotransferase and alanine aminotransferase are modestly elevated, although the ratio of aspartate aminotransferase to alanine aminotransferase is less than one, distinguishing NAFLD patients from those with alcohol-induced liver disease (Bacon et al.1994).

The International Federation of Clinical Chemistry and Laboratory Medicine established in 2002 a reference system for the measurement of enzyme activity of clinically important enzymes, including ALT, to be measured at 37 °C 23. Levels of 10-45 U/l are considered as normal, although reference values may still vary among laboratories.

The degree of elevation of transaminases does not reflect the underlying severity of the disease. The diagnosis of NAFLD can be suspected on the basis of radiological imaging such as ultrasound or magnetic resonance imaging.

However, the sensitivity of these modalities is low and often there is a significant degree of interobserver variability. A minimum of 30% of hepatocytes needs to be infiltrated by steatosis for the imaging techniques to detect fatty liver (Saadeh et al.2002).

Currently, the only method of distinguishing simple steatosis from NASH is the liver biopsy. Brunt et al (1999) proposed a grading and staging system for NASH. Grade 1 reveals mild steatosis, predominantly macrovesicular with minimal ballooning of hepatocytes and minimal inflammation. Grade 2 shows moderate steatosis, usually mixed macrovesicular and microvesicular with ballooning present in zone 3 hepatocytes, and some lobular inflammation. Grade 3 shows all the features of grade 2 plus the additional requirement of portalinflammation. Staging requires the presence of Masson trichrome stain. Stage 1 reveals zone 3 perivenular, perisinusoidal fibrosis, either focal or extensive. Stage 2 requires the features of stage 1, plus focal or extensive portal fibrosis. Stage 3, shows bridging fibrosis and stage 4 reveals cirrhosis with or without perisinusoidal fibrosis.

4. Pathogenesis

The progression from simple steatosis to steatohepatitis, fibrosis and cirrhosis is thought to be a two-hit hypothesis.

4.1 First hit

The first hit results in fat accumulation within the liver parenchyma. This occurs in abnormalities during uptake, synthesis and secretion of lipids resulting primarily from insulin resistance, which is quite common in patients with NAFLD (Marchesni et al.2001). Insulin resistance is often a primary abnormality in patients with NAFLD. There is often a genetic predisposition to insulin resistance, even in the absence of frank diabetes. Twenty per cent of the nondiabetic population may exhibit insulin resistance. Patients that exhibit more pronounced levels of insulin resistance exhibit a greater degree of steatosis (Angelico et al.2005). Central adiposity may contribute to the flow of excess free fatty acids (FFAs) to the liver by providing a direct route through the portal vein (Scheen and Luyckx. 2002). Patients with NAFLD often have risk factors such as type II diabetes, hyperlipidemia, hypertension and obesity, which are part of the insulin resistance syndrome.

Hyperinsulinemia promotes lipolysis in the adipocyte, resulting in increased FFAs delivered to the liver. In the hepatocyte, FFAs stimulate synthesis of more FFAs and inhibit oxidation of FFAs (Harrison et al.2002). The following figure 1. explains how expanded visceral mass leads to increased release of free fatty acids(FFA) from adipose tissue due to insulin resistance (IR)..

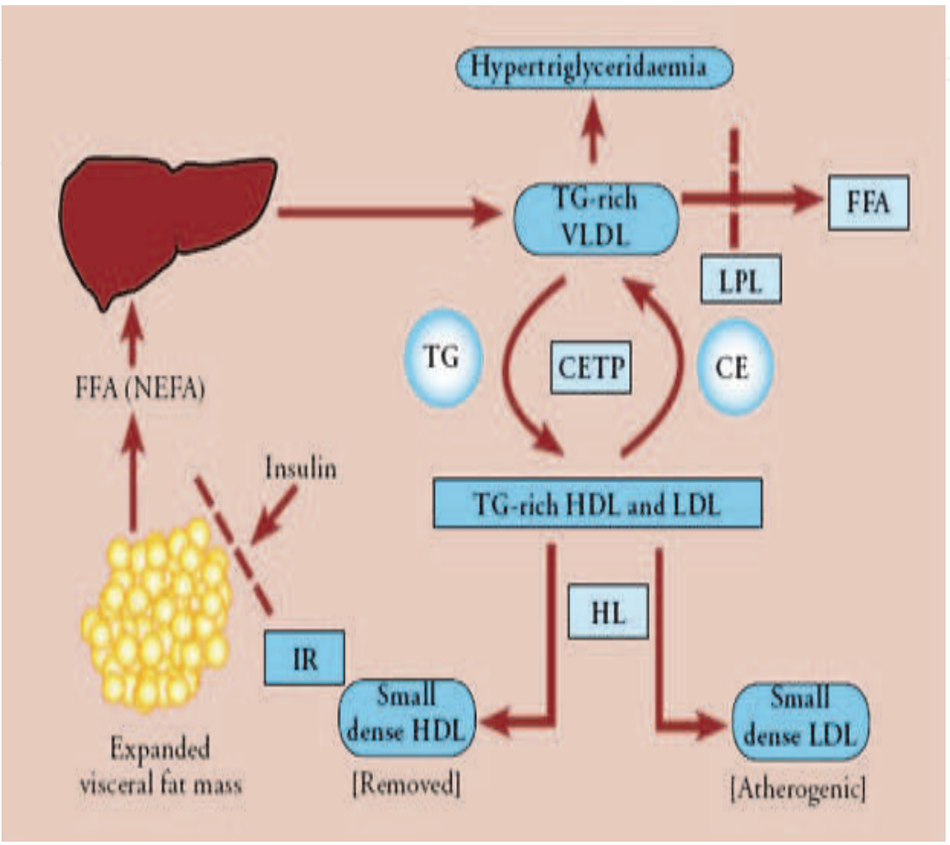


Fig. 1. Expansion of Visceral Fat Mass May Lead to Dyslipidemia and Insulin Resistance

The increased flux of free fatty acids into the liver results in the formation and secretion of very low density lipoprotein (VLDL)rich in Triglycerides. Inhibition or reduced activity of Lipoprotein lipase LPL) results in the distribution and formation of TG rich High density lipoprotein and Low density lipoprotein (LDL). Hepatic lipase acts on them to form small dense HDL and LDL (Dyslipidemia).

Insulin sensitivity is also influenced by peptide mediators, otherwise known as adipocytokines, such as tumour necrosis factoralpha (TNF-α), leptin and adiponectin and although the mechanisms by which this occurs remain largely unknown, theories are suggested. TNF-α influences steatosis by stimulating the release of FFAs from adipocytes into the liver.(Fig.2.)

TNF-α may directly induce apoptosis of hepatocytes promoting activation of hepatic stellate cells, stimulating fibrosis (Festi et al.2004). Leptin(Leptin resistance which is considered to be one of the possible third hit hypothesis) potentially may stimulate platelet-derived growth factor, ultimately leading to hepatic stellate cell proliferation resulting in fibrosis (Kejima et al.2005). Adiponectin may have a protective role against fatty liver. Recently it

was shown that adiponectin levels were significantly reduced in patients with NAFLD compared with controls resulting in an inverse relationship between insulin resistance and adiponectin levels (Saargin et al.2005). This observation may result in a future therapeutic role in the pharmacological management of NAFLD.

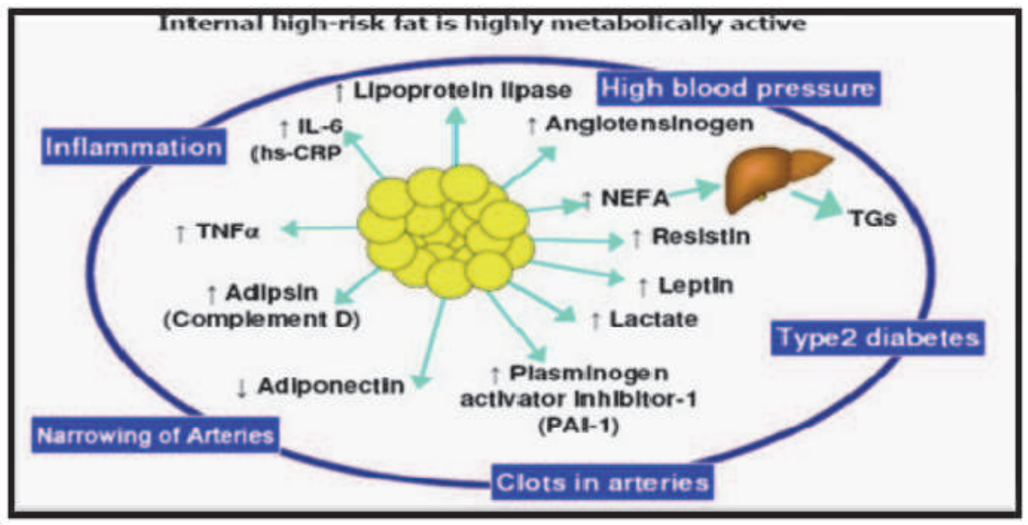


Fig. 2. Visceral Fat As a Major Site of Hormone Production, Inflammatory Markers and Its Possible Relationship including Type 2 Diabetes

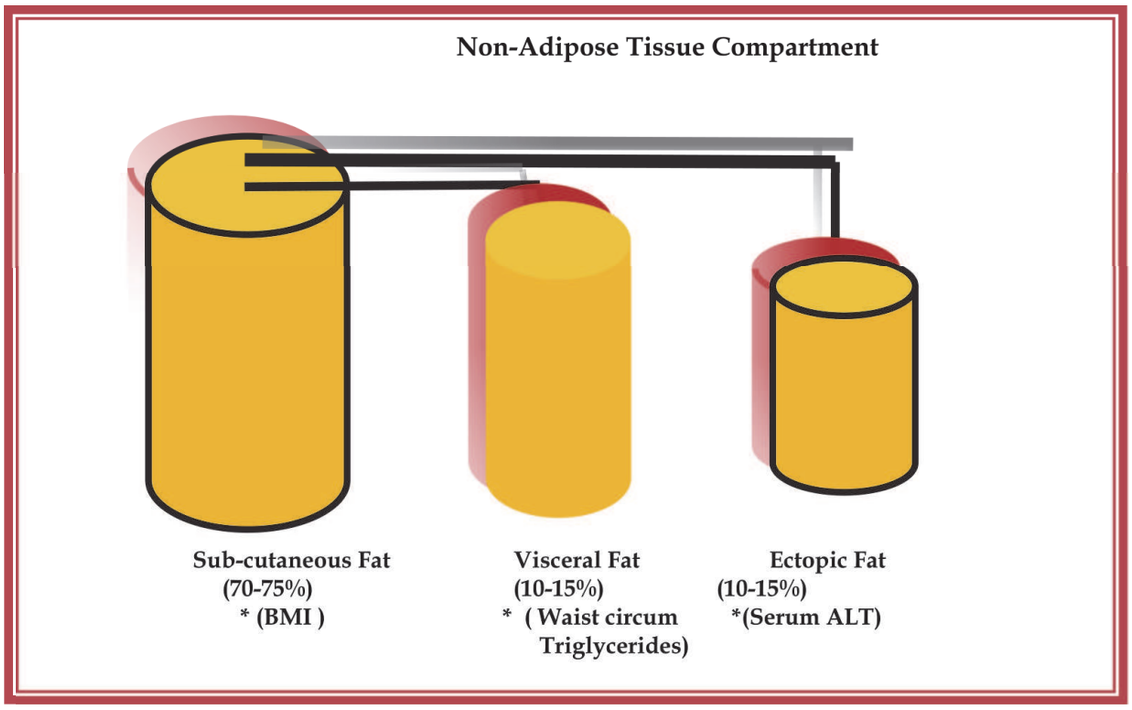
4.2 Second hit

The second hit is hepatocellular injury that results from oxidative stress, lipid peroxidation and direct cellular toxicity from FFAs (hitture and Farrell 2001). Multiple mechanisms regarding hepatocyte injury have been proposed:

1. Increased expression of cytochrome P450 isoform CYP2E1 has been shown to occur in patients with NASH. CYP2E1 is a pro-oxidant, resulting in increased production of reactive oxygen species, capable of peroxidizing cell membranes.
2. Increased insulin leads to peripheral lipolysis resulting in excess fatty acids which catalyzes lipid peroxisomes. Peroxisomes are involved in the oxidation process of fatty acids. Oxidation, along with binding and export of fatty acids, is the primary method of protecting the liver from subsequent damage.
3. The peroxisome proliferators activated receptor-alpha (PPAR-α) is responsible for regulating the esterification and export of fatty acids in very low density lipoprotein, in the binding of fatty acids and in mitochondrial and peroxisomal oxidation. Reduced expression of PPAR-α may have an important role in the pathogenesis of NASH (Yeon et al.2004).
4. Mitochondrial abnormalities have been described in patients with NASH, but not in those with simple steatosis. These mitochondrial abnormalities lead to increased mitochondrial fatty acids beta-oxidation, eventually resulting in free radical formation hepatocyte injury and steatohepatitis. Patients who are insulin resistant but do not have mitochondrial abnormalities may develop fatty liver; however, generally they do not progress to steatohepatitis (Sanyal et al.2001).

5. Methods of managing the disease

Currently, management is aimed at lifestyle modification, primarily targeting weight loss achieved through dietary modification and exercise. Additionally, treatment of all other aspects of the metabolic syndrome must be instituted. Weight loss and exercise both improve insulin resistance (Cox et al.2004), which theoretically should improve steatosis. No randomized controlled study has been run to evaluate whether histological regression occurs in patients with steatohepatitis or fibrosis after weight loss, although case reports and open-label studies suggest improvement. Weight loss should not exceed more than 1 kg per week, because rapid weight loss can exacerbate steatosis. Similarly very low calorie diets that give less than 500 kcal/day and jejunoileal bypass surgery should be avoided as a method of weight loss, due to the risk of worsening fibrosis. The recommended target for weight loss is 10% of a person's body weight over a six-month period (Angulo,2002).Multiple popular diets exist as methods of weight loss). Some diets are founded on years of medical experience, while others have deviated substantially from mainstream medical advice The Weight Watchers program is one of the traditional models, restricting portion sizes and total calories consumed. Other popular diets include carbohydrate restriction without fat restriction (Atkins diet), macronutrient and glycemic load modification (Zone diet) and fat restriction (Ornish diet). The following figure gives an idea about the distribution of fat in various compartments and the markers that indicate these compartments respectively



*As a Marker of Fat Measurement in various compartments BMI-Body Mass Index, Waist Circumference, Serum Alanine Aminotransferase (ALT)

Fig. 3. Distribution of Fat

In obese patients with BMI greater than 35 kg/m2, no significant differences were found regarding amount of weight lost at the end of one year (Dansinger et al.2005). Reduction of

cardiovascular risk factors correlated with amount of weight loss. Weight loss of 3 kg to 6 kg over one year was achieved regardless of type of diet followed. Currently, no data exist regarding various types of diets in patients with NASH.

6. Medications that could induce weight loss

Medications to reduce weight are not routinely used in the treatment of NAFLD, and have not been studied in randomized clinical trials. One case series suggested that orlistat in patients with NASH was safe, and showed significant histological improvement in both degree of steatohepatitis and fibrosis after six to 12 months of therapy (Harrison et al.2003). Orlistat is a reversible inhibitor of gastric and pancreatic lipase, and is one of two agents that have been approved for the management of obesity. This medication forms a covalent bond with the active serine residue of gastric and pancreatic lipase in the stomach and small bowel, blocking the digestion and absorption of dietary triglycerides. Orlistat in combination with a controlled energy diet, rather than diet alone, significantly increased weight loss in obese adults after one year of therapy (Davidson et al.1999).
The second approved drug in the management of obesity is sibutramine. Sibutramine was evaluated in one nonrandomized study in patients with NASH (Sabuncu et al.2003). Sibutramine in combination with a low calorie diet-induced weight loss improved insulin resistance and transaminases, as shown by ultrasonographic regression in fatty liver, compared with diet alone. It is a noradrenaline-serotonin reuptake inhibitor and produces weight loss by a dual mechanism: reduction of food intake and increase in energy expenditure. Average weight loss is in the range of 5% to 8% from baseline. Recently, rimonabant, a selective cannabinoid-1 receptor blocker, has been shown to improve cardiovascular risk factor profile and reduce body weight(Despres et al.2005). Over 1000 overweight patients with BMIs between 27 kg/m2 and 40 kg/m2 participated in this study examining the effects of rimonabant and metabolic risk factors. Mean weight loss was 6.6 kg over 12 months at a dose of 20 mg.

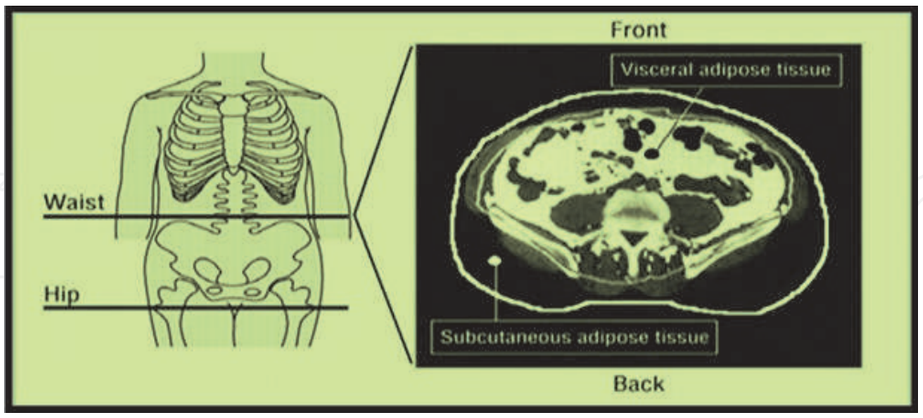


Fig. 4. WAIST HIP RATIO (WHR) AS A MEASURE OF Visceral Adiposity

Additionally, waist circumference was reduced, plasma high density lipoprotein levels increased, and plasma adiponectin levels were significantly higher in patients receiving rimonabant compared with placebo. This medication, and other weight reducing agents, may represent future therapeutic options for the pharmacological treatment of obese patients with NASH.

Certainly, diet should be combined with exercise to initiate and maintain weight loss. Exercise will enhance calorie deficit necessary for weight loss. A minimum of 30 min of moderate sustained activity five days per week is necessary to gain health benefits from exercise (28). Any fitness regimen should include a balance of aerobic exercise, strength and flexibility training

7. Pharmacotherapy for NAFLD

Currently, there are no approved pharmacological options for the treatment of NAFLD. Only three randomized controlled trials have been conducted to evaluate the efficacy of medical treatment in NAFLD (Table 3). The agents studied include antioxidants with vitamins E and C in combination, ursodeoxycholic acid and metformin. Although there was improvement in liver enzymes and steatosis in the trial evaluating metformin, there was no improvement in steatohepatitis or fibrosis at follow-up. The other two trials did not suggest any improvement in liver enzymes, steatosis, steatohepatitis or fibrosis. The remaining trials performed to date have been observational in design, had small sample size, and have had a short follow-up period. The thiazolidinediones are a class of insulin-sensitizing agents used to treat type II diabetes. Troglitazone was evaluated in an open-label trial involving 10 patients for duration of four to six months (Caldwell et al.2001). These patients had improvement in transaminases and liver histology. However, this medication was subsequently withdrawn from the market due to serious hepatic toxicity. Both rosiglitazone (Neuschwander-Tetri et al.2003) and pioglitazone (Promrat et al.2003) have been studied in open-label design, and have shown improvement in transaminases, steatosis and fibrosis. Recently VSL#3 was shown to lower markers of lipid peroxidation in patients with NASH (Loguercico et al.2005). However, larger randomized studies are needed before routine recommendation of these agents in the treatment of NASH.

Strategy	Treatment
Weight loss	Caloric restriction, exercise; sibutramine, orlistat; weight reduction surgery
Insulin-sensitizing agents	Metformin; peroxisome proliferator-activated receptor-gamma agonists (thiazolidinedione, rosiglitazone, pioglitazone)
Lipid-lowering drugs	Fibrates (gemfibrozil), fish oil
Antioxidants	*N*-acetylcysteine, vitamin E, betaine

Table. 3. Therapeutic Approaches for Nonalcoholic Fatty Liver Disease

8. Bariatric surgery

In the early age of bariatric surgery, jejunoileal bypass was the procedure most commonly performed.

A substantial proportion of patients developed advanced liver disease, presumably from bacterial overgrowth and endotoxemia in the bypassed intestine, resulting in bacterial translocation and liver disease. However, the jejunoileal bypass surgery has seldom been performed in recent years due to the multiple complications arising from this procedure. A

recent meta-analysis suggested that surgical therapy for weight loss was superior to other methods of weight loss in patients with BMI greater than 40 kg/m2 (Maggard et al.2005). This weight loss was sustained for a 10-year follow-up. Although there was a trend toward improved weight loss in patients with BMI between 35 kg/m2 and 39 kg/m2 in the surgically treated group, the data cannot be considered conclusive. Recently, one study evaluated laparascopic surgical weight loss via one of three techniques: roux-en-Y gastric bypass laparascopic adjustable gastric band and sleeve gastrectomy in patients with established NAFLD and metabolic syndrome.

Mean BMI was 56 kg/m2 (Mattar et al.2005). Patients had liver biopsies at the time of the bariatric surgery followed by a repeat biopsy after 15 months. Mean excess weight loss at the time of the second biopsy was 59%. There was a marked improvement in live steatosis, steatohepatitis and fibrosis. In fact, in some patients, inflammation and fibrosis completely resolved. Additionally, there was improvement in the metabolic risk factor profile.

Hence, as newer methods of bariatric surgery become more popular, there may be a future role for this type of surgery in morbidly obese patients with NASH.

9. Whether liver biopsy is mandatory?

Often, NAFLD is a diagnosis of exclusion. Patients are given advice regarding lifestyle modifications and re-evaluated clinically and biochemically several months later in routine follow-up. This may be a reasonable approach for the time being because there are no effective medications in the treatment of NAFLD. However, as pharmacotherapy becomes an option in the future, this line of thought may need to be revised. The distinction between pure fatty change and steatohepatitis can only be made histologically. This distinction is important because NAFLD has a benign prognosis, whereas NASH progresses toward cirrhosis. Because of the risk of NASH in patients suspected to have fatty liver, it could be argued that all patients should be offered a liver biopsy to stage the disease. However, in terms of logistics, cost and side effects, this may not be possible. Hence, it is reasonable to biopsy patients with risk factors for more advanced disease such as advancing age, obesity, hypertension and diabetes mellitus. Additionally, the liver biopsy may occasionally reveal unsuspected abnormalities indicating an alternate or additional diagnosis to fatty liver(Younossi, 2008).

10. Conclusions

Obesity epidemic is a global phenomena carrying with the risk of precipitating insulin resistant states including NAFLD which is shown to be on the rise. The primary abnormality for NAFLD reported is that of intrinsic insulin resistance. Therefore NAFLD could be one of the risk factors for the development of Type II Diabetes (Guido et al.2011). There seems to be no approved pharmacological therapies for the treatment of NASH. The major suggested treatment continues to be weight loss therapy through diet and exercise, and aggressive risk factor control.

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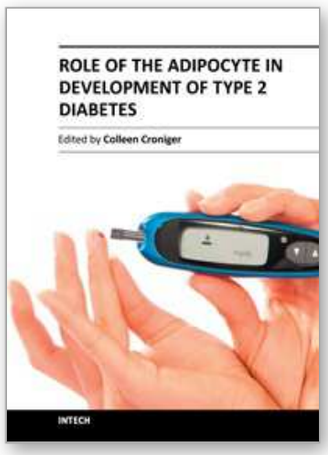

Role of the Adipocyte in Development of Type 2 Diabetes

Edited by Dr. Colleen Croniger

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Adipocytes are important in the body for maintaining proper energy balance by storing excess energy as triglycerides. However, efforts of the last decade have identified several molecules that are secreted from adipocytes, such as leptin, which are involved in signaling between tissues and organs. These adipokines are important in overall regulation of energy metabolism and can regulate body composition as well as glucose homeostasis. Excess lipid storage in tissues other than adipose can result in development of diabetes and nonalcoholic fatty liver disease (NAFLD). In this book we review the role of adipocytes in development of insulin resistance, type 2 diabetes and NAFLD. Because type 2 diabetes has been suggested to be a disease of inflammation we included several chapters on the mechanism of inflammation modulating organ injury. Finally, we conclude with a review on exercise and nutrient regulation for the treatment of type 2 diabetes and its co-morbidities.

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